UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/784,528 | 02/23/2004 | Arthur M. Brown | 22884/04085 | 1521 |

24024 7590 03/27/2007

CALFEE HALTER & GRISWOLD, LLP
800 SUPERIOR AVENUE
SUITE 1400
CLEVELAND, OH 44114

| EXAMINER | |
|---|---|
| SAJJADI, FEREYDOUN GHOTB | |
| ART UNIT | PAPER NUMBER |
| 1633 | |

| SHORTENED STATUTORY PERIOD OF RESPONSE | MAIL DATE | DELIVERY MODE |
|---|---|---|
| 3 MONTHS | 03/27/2007 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/784,528 | BROWN ET AL. | |
| | Examiner | Art Unit | |
| | Fereydoun G. Sajjadi | 1633 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *24 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-23* is/are pending in the application.

4a) Of the above claim(s) *20-23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *2/23/2004* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/20/04 & 1/19/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

UNITED STATES PATENT AND TRADEMARK OFFICE

COMMISSIONER FOR PATENTS
UNITED STATES PATENT AND TRADEMARK OFFICE
WASHINGTON, DC 20231
www.uspto.gov

| APPLICATION NO. /CONTROL NO. | FILING DATE | FIRST NAMED INVENTOR / PATENT IN REEXAMINATION | ATTORNEY DOCKET NO. |
|---|---|---|---|
| 10/784,528 | 2/23/2004 | Arthur Brown | 22884/04085 |

| EXAMINER | |
|---|---|
| Fereydoun G. Sajjadi | |
| **ART UNIT** | **PAPER** |
| 1633 | |

**DATE MAILED:**

**Please find below and/or attached an Office communication concerning this application or proceeding.**

**Commissioner of Patents**

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth below or on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. Sequence identifiers are missing for some of the sequences listed in the specification. Applicant is required to thoroughly review the specification and comply with all sequence rules. For example, the following sequences in the specification do not have sequence identifiers: the amino acid sequences recited in the sequence alignments of Figure 10, do not include sequence identifiers. No corresponding SEQ ID NOS are present in the brief description of said Figures either.

Applicant is given ONE MONTH, or THIRTY DAYS, whichever is longer, from the mailing date of this letter within which to comply with the sequence rules, 37 CFR 1.821 - 1.825. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 CFR 1.821(g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a). In no case may an applicant extend the period for reply beyond the SIX MONTH statutory period. Direct the reply to the undersigned. Applicant is requested to return a copy of the attached Notice to Comply with the reply.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Fereydoun G. Sajjadi whose telephone number is **(571) 272-3311**. The examiner can normally be reached Monday through Friday, between 7:00 am-4:00 pm EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on **(571) 272-0739**. The fax phone number for the organization where this application or proceeding is assigned is **(571) 273-8300**. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at (866) 217-9197 (toll-free).

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

**For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.**

Fereydoun G. Sajjadi, Ph.D.
Examiner, Art Unit 1633

## DETAILED ACTION

Applicant's response of January 24, 2007, to the Restriction Requirement dated September 25, 2006 has been entered. No claims were cancelled, amended, or newly added. Claims 1-23 are pending in the application.

### *Election/Restrictions*

Applicants' election of Group IX (claims 11-13 and 15-19) without traverse, drawn to a method for inducing apoptosis or treating cancer which is epithelial carcinoma, using a human KChAP protein or variant thereof, and the encoding nucleic acid, is acknowledged.

Upon further consideration, the previous restriction between Groups I-XII is hereby withdrawn. Thus claims 1-10 and 14 are rejoined and will be examined to the extent that the claims encompass the elected invention.

Claims 20-23 are withdrawn from further consideration by the Examiner, pursuant to 37 CFR 1.142(b), as being drawn to non-elected inventions. The requirement for restriction between Groups I-XII and XIII-XV is maintained and hereby made FINAL.

Please note that after a final requirement for restriction, the Applicants, in addition to making any response due on the remainder of the action, may petition the Commissioner to review the requirement. Petition may be deferred until after final action on or allowance of claims to the invention elected, but must be filed not later than appeal. A petition will not be considered if reconsideration of the requirement was not requested. (See § 1.181.).

Applicant timely responded to the restriction (election) requirement in the Paper filed January 24, 2007. Claims 1-19 are currently under examination.

### *Objection to Drawings & Failure to Comply with Nucleotide and /or Amino Acid Sequence Disclosures 37CFR §1.821-1.825s*

37 CFR 1.821 (a) states: Nucleotide and/or amino acid sequences as used in §§1.821 through 1.825 are interpreted to mean an unbranched sequence of four or more amino acids or an unbranched sequence of ten or more nucleotides. 37 CFR 1.821 (d) states: Where the description or claims of a patent application discuss a sequence that is set forth in the "Sequence

Listing " in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO: " in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application.

Neither the sequences depicted in Fig. 10, nor the description of the drawing (p. 7), refer to the sequences of the PIAS family by SEQ ID NO. As it is not clear whether the sequences of Figure 10 are present in the CRF listing, Applicant is required to check both the as filed paper and CRF sequence listings to ensure concordance with the sequences disclosed in the specification. If the sequences are present in the sequence listing as filed, the instant application may be placed in compliance with 37 CFR 1.821-1.825 by amending the brief description of the drawings in the specification to refer to the primer sequences by appropriate SEQ ID NOS. If the sequences are not present, then new paper and CRF sequences are required. See the notice to comply with the Sequence Rules set forth in 37CFR §1.821-1.825, included with this action.

***Claim Objections***

Claims 1-10 are objected to as being incomplete. The claims are directed to methods of inducing apoptosis in human hyperproliferative or cancer cells comprising contacting said cells with either a human KChAP protein or a nucleic acid encoding said protein. However, the elected method of the invention comprises contacting cells with a human KChAP protein and a nucleic acid encoding said protein. Appropriate correction is required.

***Claim Rejections - 35 USC § 112- Second Paragraph***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 4 and 19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 4 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: contacting the cells with a KChAP protein or a nucleic acid encoding KChAP protein such that the protein or nucleic acid is taken up by said cells. Thus it is not clear how said administering may result in any form of treatment.

Claim 19 recite the limitation "the active agent" in the first line of the claim. There is insufficient antecedent basis for this limitation in the claim. Base claim 11 refers to an agent, an active variant and an active KCHAP related protein, but not an active agent.

***Claim Rejections - 35 USC § 112, Written Description***

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-19 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims embrace methods of inducing apoptosis in cells comprising increasing the levels of numerous variants and proteins related to KChAP, and expression of nucleic acid encoding the same. As such, the numerous variants and proteins related to KChAP constitute a claimed genus that encompasses other proteins with the ability to alter $K^+$ levels in cells and further induce apoptosis, yet to be discovered.

The instant specification states that KChAP variants increase efflux, cause cell shrinkage and activate caspase 3 to produce PARP cleavage. In addition, the KChAP variant has at least about 80% amino acid sequence identity to the sequence of KChAP protein and include protein wherein one or more amino acid residues are added or deleted at the N-or C-terminus, or one or more amino acid residues are substituted within (paragraphs [0054], pp. 11-12). However, no such examples or descriptions of the possible derived sequences or alterations in the sequences of KChAP variants or related proteins that are further capable of inducing apoptosis are in fact

presented. The specification is further silent on which amino acid alterations would retain an KChAP activity. The specification merely discloses the sequence for the human, KChAP gene and deduced amino acid sequence (SEQ ID NOS: 1 and 2, respectively), having the ability to induce apoptosis in human cell lines.

Thus, the disclosed structural features of the KChAP gene and encoded protein do not constitute a substantial portion of the claimed genus. As such, the Artisan of skill could not predict that Applicant possessed any additional species, except for the human KChAP gene, having the ability to induce apoptosis. Hence, only full length and the human KCAP gene and protein could be demonstrated as possessed.

To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail such that the Artisan can reasonably conclude that the inventor(s) had possession of the claimed invention. Such possession may be demonstrated by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and/or formulae that fully set forth the claimed invention. Possession may be shown by an actual reduction to practice, showing that the invention was "ready for patenting", or by describing distinguishing identifying characteristics sufficient to show that Applicant was in possession of the claimed invention (January 5, 2001 Fed. Reg., Vol. 66, No. 4, pp. 1099-11). Moreover, MPEP 2163 states:

[A] biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence.

Overall, what these statements indicate is that the Applicant must provide adequate description of such core structure and function related to that core structure such that the Artisan of skill could determine the desired effect. Hence, the analysis above demonstrates that Applicant has not determined the core structure for full scope of the claimed genus.

In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. Therefore, the breadth of the claim as reading on altering the amino acid sequence of numerous proteins, using an enormous number of sequences variations, including

KChAP variants and related proteins yet to be discovered; in view of the level of knowledge or skill in the art at the time of the invention, an Artisan of skill would not recognize from the disclosure that Applicant was in possession of the genus of the numerous amino acid variants of the KChAP protein. Thus it is concluded that the written description requirement is not satisfied for the claimed genus.

In conclusion, this limited information is not deemed sufficient to reasonably convey to one skilled in the art that Applicant is in possession of a significant number of KChAP variants and related proteins, the amino acid sequences for which could be altered by one or more amino acids; at the time the application was filed. Thus it is concluded that the written description requirement is not satisfied for the claimed genus.

***Claim Rejections - 35 USC § 112-Scope of Enablement***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-19 are rejected under 35 U.S.C.§112, first paragraph, because the specification, while being enabling for a method of inducing apoptosis in cultured cancer cell lines, comprising the step of introducing into said cells an expression vector comprising a nucleic acid encoding a human KChAP protein as set forth in SEQ ID NO: 1, said nucleic acid operably linked to a promoter active in cancer cell lines, does not reasonably provide an enablement for a method of inducing apoptosis in human hyperproliferative cells or treating a subject with a hyperproliferative disorder, said methods comprising contacting cells with a human KChAP protein or variants of KCHAP protein or proteins related thereto, in combination with nucleic acids encoding said KChAP protein, related proteins and variants having at least 90% identity to the human KChAP protein, as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

This rejection is based on several issues related to the absence of an enabling disclosure for the methods of inducing apoptosis in any hyperproliferative human cells *in vivo*, comprising contacting said cells with human KChAP proteins or its variants or proteins related thereto. The rejection is further based on the absence of an enabling disclosure for the method of treating a subject with a hyperproliferative disease comprising administering a pharmaceutical composition comprising human KChAP proteins or its variants or proteins related thereto and nucleic acids encoding the same. In determining whether Applicant's claims are enabled, it must be found that one of skill in the art at the time of invention by Applicant would not have had to perform "undue experimentation" to make and/or use the invention claimed. Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404:

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

MPEP § 2164.04 states: "[W]hile the analysis and conclusion of a lack of enablement are based on the factors discussed in MPEP § 2164.01(a) and the evidence as a whole, it is not necessary to discuss each factor in the written enablement rejection."

The instant claims embrace methods of inducing apoptosis and treating hyperproliferative disease by contacting human cells with KChAP protein, or its variants or proteins related thereto, in addition to introducing into said cells nucleic acids encoding said KChAP protein, variants and related proteins.

The specification discloses that infection of prostate or breast cancer cell lines with an adenovirus vector encoding human KChAP (Ad/KChAP) induces apoptosis in these cells, regardless the presence of p53 proteins (Examples 1-2; pp. 25-30). The specification further discloses that injection of the adenovirus vector encoding human KChAP into tumors formed by

human prostate cancer cells Du145 and LNCaP in nude mice suppresses tumor growth (Example 3, pp. 31-32 ).

The specification is silent on the induction of apoptosis by any variants of human KChAP protein or proteins related to KChAP protein. The specification is further silent on the treatment of any other hyperproliferative disorder in a subject. Moreover, the instant disclosure is devoid of any induction of apoptosis in any cell by contacting said cell with a human KChAP protein, either alone or in combination with Ad/KChAP vector. Furthermore, it is not clear how the levels of KChAP protein may be increased in the cells without a mechanism facilitating their uptake. It is further not clear by what level said increase in intracellular KChAP protein is sufficient to induce apoptosis.

Regarding the administration of KChAP nucleic acid to the cells, the instant claims embrace administration of any nucleic acid encoding human KChAP to a subject, that would include administration of naked plasmid DNA administered by any route, including systemic administration. While the specification describes the intratumoral injection of Ad/KChAp vector, the instant disclosure is silent on any other vector system or any other method of administration. Thus, it is not clear how administration of a naked plasmid expression vector by a systemic route could deliver sufficient KChAP to the site or tumor and further, avoid non-specific delivery to normal cells, thus causing unwanted apoptosis.

The prior art at the time of filing did not teach the induction of apoptosis in hyperproliferative human cells by increasing the levels of any KChAP protein variant, or proteins related thereto. Bowie, et al. (Science, 247: 1306-10, 1990) provide notable insight into the lack of reasonable predictability for the mutation of any particular protein. To wit, Bowie discuses that while many substitutions may be tolerated, in other cases substitutions may not be tolerated at all (e.g., 1306, col. 2, paragraph 2). Moreover, the significance of surface and buried amino acids while is not reasonably predictable either (pp. 1306-07), surface sites may not have any importance, but sometimes they are absolutely important due to binding (p. 1308), and predicting structure with reasonable predictability is generally limited to homologous proteins, but even that is difficult due to alignment problems (p. 1308). Bowie continues: it is not reasonably predictable that any particular amino acid change, deletion, or addition would provide a functional molecule with similar activity, and only painstaking analysis would provide such

information for any particular change (e.g., pp. 1309-10). These observations have been further supported by the findings of Skolnick et al. (TIBTECH 18:34-39, 2000), stating: "Knowing a protein's structure does not necessarily tell you its function" (Box 2, p. 36), noting that "alternatives are needed to assign the biochemical function of the 30-50% of proteins whose function cannot be assigned by any current methods" (second column, p. 37).

Hence, the nature of the invention is not reasonably predictable for any of the numerous numbers of possible proteins claimed, due to the unpredictability of structure-function relationships. Moreover, given the lack of reasonable predictability between structure and function, the identification and subsequent analysis for apoptotic activity of each KChAP variant or related protein, would require further and undue experimentation.

Regarding the use of nude mice as the in vivo model of human cancer, the prior art of Kerbel (Cancer & Metastasis Rev. 17:301-304; 1999), teaches that "Most transplantable tumor therapy experiments utilize ectopic (usually subcutaneous) injection and growth of the cells. The positive responses of such tumors to certain anti-cancer drugs or therapies have been questioned, and at least in some cases it has been shown that orthotopically transplanted tumors do not necessarily recapitulate the 'encouraging' responses of their ectopically grown counterparts...The response to therapy of a single 'primary'(usually ectopic/subcutaneous) growing transplanted tumor mass is usually what is evaluated rather than that of distant metastases growing in visceral organs such as the brain, lungs, or liver. Clearly this is not representative of most clinical treatment situations in which distant metastases are the target of systemic therapy, and not the primary tumor, which is generally dealt with using surgery. Given recent findings that various properties of tumor cells can be influenced by the organ microenvironment [15], there is clearly a need to place more emphasis on tumor models in which metastases are the primary target of therapy, and not just a transplanted 'primary' tumor." (first column, p. 302). In the instant case, Applicants have not utilized primary tumor cells and have further administered the cells hetertopically.

The specification is silent on the description for orthotopic administration of the cell lines and is further silent on the detection of micrometastases of any tumors, to any sites, including bone marrow. As the culture modified cell lines described do not constitute human primary tumor cells, or the morphological characteristics of human cancers, together with the lack of

orthotopic transplantation of cells, the metastases described fail to adequately reflect or simulate the progression of human cancer.

At the time of filing, the prior art taught the importance of orthotopic transplantation of tumor cells in developing animal models of tumor growth that accurately recapitulate the growth and metastases of the tumor in the original host mammal. Vieweg et al. (first column, p. 196; Cancer Investigation, 13(2):193-201; 1995) disclose: "the site of tumor implantation can greatly influence biological properties and immunological responsiveness to treatment", and that, "appropriate animal models should be based on the choice of a highly relevant animal tumor model that corresponds in its origin and tumor biology with a particular form of human cancer as well as on orthotopic implantation of the tumor cells into their organ of origin." Additionally, Hoffman (Invest. New Drugs 17: 343-360; 1999) notes that "Currently used rodent tumor models, including transgenic tumor models, or subcutaneously-growing human tumors in immunodeficient mice, do not sufficiently represent clinical cancer, especially with regard to metastasis and drug sensitivity. In order to obtain clinically accurate models, we have developed the technique of surgical orthotopic implantation (SOI) to transplant histologically-intact fragments of human cancer, including tumors obtained directly from the patient, to the corresponding organ" (Abstract). Thus, Hoffman emphasized the importance of using orthotopically transplanted primary tumor tissue to produce an accurate model of clinical cancer.

The instantly claimed methods rely on the activity of KChAP protein in cells to induced apoptosis. In a post-filing review of the role of $K^+$ channels in regulating tumor cell proliferation and apoptosis (Wang, Eur. J. Physiol. 448:274-286; 2004), the author states: "$K^+$ channels favor tumor cell proliferation, therefore, inhibition of $K^+$ channel function or down-regulation of $K^+$ channel expression should inhibit tumorigenesis...On the other hand, $K^+$ channels also promote apoptotic cell death...enhancement of $K^+$ channel activity can facilitate not only tumor cell apoptosis but also tumor cell proliferation. This apparent paradox confounds the manipulation of $K^+$ channel function and/or expression as an option for the treatment of cancers." (pp. 281-282 bridging). The foregoing is especially relevant in view of the non-specific delivery of the KChAP protein that may result as a consequence of the routes of delivery encompassed by the instant claims and further questions the validity of the claimed methods as a therapeutic.

The guidance provided by the specification amounts to an invitation for the skilled Artisan to try and follow the disclosed instructions to make and use the claimed invention. The specification merely demonstrates the apoptotic activity of the human KChAP protein expression in cancer related cell lines.

The detail of the disclosure provided by Applicant, in view of the prior art, must encompass a wide knowledge, so that the Artisan of skill would be able to practice the invention as claimed by Applicant, without undue burden being imposed on such Artisan. This burden has not been met because it would require undue experimentation to specifically induce apoptosis limited to hyperproliferative cells via the intracellular elevation KChAP protein, or to treat a subject with a hyperproliferative disease, as claimed in the instant application.

Therefore, in view of the art recognized high level of unpredictability regarding the use of cell lines in extrapolating results to an *in vivo* setting, together with the large quantity of research required to define these unpredictable variables, and the lack of guidance provided in the specification regarding the delivery of KChAP protein to cells, it is the position of the examiner that it would require undue experimentation for one of skill in the art to practice the scope of the invention as broadly claimed. Hence, absent a strong showing by Applicant, in the way of specific guidance and direction, and/or working examples demonstrating the same, such invention as claimed by Applicant is not enabled.

## *Conclusion*

**Claims 1-19 are not allowed.**

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Fereydoun G. Sajjadi whose telephone number is (571) 272-3311. The examiner can normally be reached on 7:00-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Fereydoun G. Sajjadi, Ph.D.
Examiner, AU 1633

AU 1633

| Notice to Comply | Application No. 10/784,528 | Applicant(s) Brown et al. | |
|---|---|---|---|
| | Examiner Fereydoun Sajjadi | Art Unit 1633 | |

## NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e). Therefore a search of the correct sequence is not possible.

☒ 7. Other: The specification contains amino acid sequences without SEQ ID NO identifiers.

**Applicant Must Provide:**

☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☒ An initial or substitute paper copy of the "Sequence Listing", **as well as an amendment specifically directing its entry into the application**.

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216 or (703) 308-2923
For CRF Submission Help, call (703) 308-4212 or 308-2923
PatentIn Software Program Support
Technical Assistance.....703-287-0200
To Purchase PatentIn Software.....703-306-2600

**PLEASE RETURN A COPY OF THIS NOTICE WITH YOUR REPLY**